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☐	L1	botulinum.clm. and (epitop$.clm. or $tope.clm.)	20

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Search Results - Record(s) 1 through 20 of 20 returned.

☐ 1. 20050158323. 06 Dec 04. 21 Jul 05. Methods of killing tumor cells by targeting internal antigens exposed on apoptotic tumor cells. Evans, Elizabeth E., et al. 424/155.1; 435/320.1 435/334 435/69.1 435/7.23 530/388.8 536/23.53 G01N033/574 C07H021/04 A61K039/395 C07K016/30 C12N005/06.

☐ 2. 20050136049. 26 Jul 03. 23 Jun 05. Binding constructs and methods for use thereof. Ledbetter, Jeffrey A., et al. 424/132.1; 530/387.3 A61K039/395 C07K016/44.

☐ 3. 20050118182. 23 Mar 04. 02 Jun 05. Mutated anti-cd22 antibodies with increased affinity to cd22-expressing leukemia cells. Pastan, Ira H, et al. 424/178.1; 424/239.1 530/391.1 A61K039/40 C07K016/46.

☐ 4. 20040241702. 12 May 04. 02 Dec 04. Gene expressed in prostate cancer and methods of use. Pastan, Ira H., et al. 435/6; 435/320.1 435/325 435/69.3 530/350 536/23.5 C12Q001/68 C07H021/04 C07K014/705.

☐ 5. 20040219619. 16 Jan 04. 04 Nov 04. Methods of identifying compounds that alter toxin persistence and/or protease activity. Fernandez-Salas, Ester, et al. 435/7.32; 424/239.1 G01N033/554 G01N033/569 A61K039/08.

☐ 6. 20040175385. 01 Aug 03. 09 Sep 04. Therapeutic monoclonal antibodies that neutralize botulinum neurotoxins. Marks, James D., et al. 424/164.1; 435/7.32 530/388.4 A61K039/40 G01N033/554 G01N033/569.

☐ 7. 20040147716. 02 Jul 03. 29 Jul 04. Peptides comprising aromatic D-amino acids and methods of use. Anderson, Byron E.. 530/329; 530/330 C07K007/06.

☐ 8. 20040136959. 08 Jul 03. 15 Jul 04. Sensitization of cancer cells to immunoconjugate-induced cell death by transfection with il -13 receptor alpha chain. Puri, Raj K.. 424/93.2; 514/44 A61K048/00.

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☐ 10. 20040038307. 12 May 03. 26 Feb 04. Unique recognition sequences and methods of use thereof in protein analysis. Lee, Frank D., et al. 435/7.1; 435/6 702/19 C12Q001/68 G01N033/53 G06F019/00 G01N033/48 G01N033/50.

☐ 11. 20040013687. 02 Jun 03. 22 Jan 04. Compositions and methods for transepithelial molecular transport. Simpson, Lance, et al. 424/190.1; A61K039/02.

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☐ 13. 20030211471. 14 Apr 03. 13 Nov 03. Method for detecting ligands and targets in a mixture.

Hammond, David J., et al. 435/5; 435/6 435/7.2 435/7.31 435/7.32 435/7.93 C12Q001/70 C12Q001/68 G01N033/53 G01N033/567 G01N033/569 G01N033/554 G01N033/537 G01N033/543.

☐ 14. 20030088074. 28 May 02. 08 May 03. Recombinant bivalent monospecific immunoglobulin having at least two variable fragments of heavy chains of an immunoglobulin devoid of light chains. Hamers, Raymond, et al. 530/387.1; C07K016/00.

☐ 15. 20030009025. 20 Jul 01. 09 Jan 03. Recombinant vaccine against botulinum neurotoxin. Smith, Leonard A., et al. 536/23.7; 435/252.3 435/254.23 435/320.1 435/69.1 C07H021/04 C12P021/02 C12N001/21 C12N001/18.

☐ 16. 20020155114. 31 Aug 98. 24 Oct 02. THERAPEUTIC MONOCLONAL ANTIBODIES THAT NEUTRALIZE BOTULINUM NEUROTOXINS. MARKS, JAMES D., et al. 424/150.1; A61K039/40.

☐ 17. 6342215. 01 Dec 98; 29 Jan 02. Identification of genes. Holden; David William, et al. 424/93.2; 435/252.1 435/252.4 530/350 536/23.7. A61K048/00 C12N001/20 C12N015/31 C07K014/255.

☐ 18. 6270777. 20 Dec 96; 07 Aug 01. Conserved metalloprotease epitopes. Sokol; Pamela A., et al. 424/260.1; 424/130.1 424/184.1 424/185.1 424/190.1 424/197.11 424/234.1 424/246.1 424/261.1 424/94.67 530/300 530/324 530/325 530/326 530/327 530/328 530/350 530/387.1. A61K039/104 A61K039/02 C07K014/195 C07K014/21.

☐ 19. 5989545. 12 Jan 98; 23 Nov 99. Clostridial toxin derivatives able to modify peripheral sensory afferent functions. Foster; Keith Alan, et al. 424/183.1; 424/832 424/94.67 435/220 435/69.1 435/69.7 514/2 530/350 530/388.22 530/391.7 530/402. A61K038/16 C07K014/33 C07K019/00 C12N015/62.

☐ 20. 5387503. 12 Nov 92; 07 Feb 95. Assay method using internal calibration to measure the amount of analyte in a sample. Selmer; Johan, et al. 435/5; 435/7.2 435/7.21 435/7.23 435/7.32 435/7.4 435/7.8 435/7.94 435/7.95 435/967 435/975 436/501 436/518 436/807. G01N033/543 G01N033/566 G01N033/569.

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Term	Documents
BOTULINUM	2892
BOTULINUMS	0
EPITOP$	0
EPITOP	50
EPITOPAL	19
EPITOPALLY	4
EPITOPAL-BINDING	1
EPITOPAL-HYPERVARIABLE	1
EPITOPC	10
EPITOPCS	7

EPITOPDES	2
(BOTULINUM.CLM. AND (EPITOP$.CLM. OR $TOPE.CLM.)).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	20

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TITLE: Recombinant vaccine against botulinum neurotoxin

CLAIMS:

1. A nucleic acid encoding the carboxy-tenninal portion of the heavy chain (H.sub.C) of botulinum neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT serotype C.sub.1, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G, wherein said nucleic acid is expressable in a recombinant organism selected from Escherichia coli and Pichia pastoris.

4. A nucleic acid encoding the amino-terminal portion of the heavy chain (H.sub.N) of botulinum neurotoxin (BONT) selected from the group consisting of BONT serotype B, BONT serotype C.sub.1, BONT serotype D, BONT serotype E, BONT serotype F, and BoNT serotype G, wherein said nucleic acid is expressable in a recombinant organism selected from Escherichia coli and Pichia pastoris.

12. The nucleic acid of any one of claims 1, 3, 4, or 6, wherein said nucleic acid encoding H.sub.C or H.sub.N is expressed in a recombinant host organism with higher yield than a second nucleic acid fragment encoding the same H.sub.C sequence, said second nucleic acid fragment having the wild-type Clostridum botulinum sequence of H.sub.C.

14. A method of preparing a polypeptide comprising the carboxy-terminal portion of the heavy chain (H.sub.C) of botulinum neurotoxin (BoNT) or the amino-terminal portion of the heavy chain (H.sub.N) of botulinum neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT serotype C, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G, said method comprising culturing a recombinant host organism transfected with the expression vector of claim 13 under conditions wherein H.sub.C or H.sub.N is expressed.

18. An immunogenic composition comprising the carboxy-terminal portion of the heavy chain (H.sub.C) of botulinum neurotoxin (BONT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT serotype C, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G.

21. An immunogenic composition comprising the amino-terminal portion of the heavy chain (H.sub.N) of botulinum neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT serotype C, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G.

24. An immunogenic composition comprising a polypeptide comprising epitopes contained in the carboxy-terminal portion of the heavy chain (H.sub.C) of botulinum neurotoxin (BoNT) or the amino-terminal portion of the heavy chain (H.sub.N) of botulinum neurotoxin (BoNT) selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT serotype C, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G, said epitopes eliciting protective immunity toward the respective BoNT serotype.

26. An immunogenic composition comprising a protein containing at least a portion of a botulinum neurotxin (BoNT) sequence, said BoNT being selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT serotype C, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G.

31. A nucleic acid encoding a protein containing at least a portion of a botulinum neurotxin (BONT)

sequence, said BoNT being selected from the group consisting of BoNT serotype A, BoNT serotype B, BoNT serotype C, BoNT serotype D, BoNT serotype E, BoNT serotype F, and BoNT serotype G.

34. A recombinant host cell containing the expression vector of claim 33.

35 The recombinant host cell of claim 34, wherein said host cell expresses a protein containing at least a portion of BoNT sequence, said portion of BoNT sequence containing at least one protective epitope of the respective BoNT serotype.

J Protein Chem. 1996 Oct;15(7):691-700. Related Articles, Links

Mapping of the antibody-binding regions on botulinum neurotoxin H-chain domain 855-1296 with antitoxin antibodies from three host species.

Atassi MZ, Dolimbek BZ, Hayakari M, Middlebrook JL, Whitney B, Oshima M.

Verma and Marrs McLean Department of Biochemistry, Baylor College of Medicine, Houston, Texas 77030, USA.

Botulism due to food poisoning is caused mainly by protein toxins, botulinum neurotoxins (BoNTs), produced by Clostridium botluinum in seven known immunological serotypes. These are the most potent toxins and poisons known. BoNT effects blockade of neuromuscular transmission by preventing neurotransmitter release. Human botulism is most frequently caused by types A, B, and E. Recent studies have shown that immunization with a 43-kDa C-terminal fragment (Hc, residues 860-1296) of BoNT/A affords excellent protection against BoNT/A poisoning. We raised antibodies (Abs) against BoNT/A in horse, and against pentavalent toxoid (BoNTs A, B, C, D, E) in human volunteers and outbred mice. Thirty-one 19-residue peptides that started at residue 855, overlapped consecutively by 5 residues, and encompassed the entire length of the Hc of BoNT/A were synthesized and used for mapping the Ab-binding regions recognized by the anti-BoNT/A antisera. Horse Abs against BoBT/A were bound by peptides 855-873, 939-957, 1079-1097/1093-1111 overlap, 1191-1209/1205-1223 overlap, 1261-1279 and 1275-1296. In addition, peptides 883-901, 911-929, 995-1013, 1023-1041/1037-1055 overlap, 1121-1139, and 1149-1167 gave low, but significant and reproducible, binding. With human antisera, high amounts of Abs were bound by peptides 869-887, 925-943, 981-999, 995-1013, 1051-1069, and 1177-1195. In addition, lower amounts of Abs were bound by peptides 911-929, 939-957, 967-985, and the overlaps 1121-1139/1135-1153 and 1247-1265/1261-1279/1275-1296. With outbred mouse antisera, high amounts of Abs were bound by peptides 869-887, 1051-1069, and 1177-1195, while peptides 939-957, 995-1013, 1093-1111, and 1275-1296 bound lower amounts of Abs. The results indicate that horse antiserum against BoNT/A or human and mouse (outbred) antisera against the toxoid recognized similar regions on BoNT/A, but exhibited some boundary frame shifts and differences in immunodominance of these regions among the antisera. Selected synthetic epitopes will be used as immunogens to stimulate active or passive (by Ab transfer) immunity against toxin poisoning.

PMID: 8968960 [PubMed - indexed for MEDLINE]

Immunol Invest. 1997 Jun;26(4):491-504. Related Articles, Links

Localization of the regions on the C-terminal domain of the heavy chain of botulinum A recognized by T lymphocytes and by antibodies after immunization of mice with pentavalent toxoid.

Rosenberg JS, Middlebrook JL, Atassi MZ.

Department of Biochemistry, Baylor College of Medicine, Houston, TX 77030, USA.

We have mapped the regions recognized by T and/or B cells (Abs) on the C-terminal domain (Hc) of the heavy chain of botulinum neurotoxin serotype A (BoNT/A) after immunization of two inbred mouse strains with pentavalent toxoid (BoNTs A, B, C, D and E). Using a set of synthetic overlapping peptides, encompassing the entire Hc domain (residues 855-1296), we demonstrated that T cells of Balb/c (H-2d) mice, primed with one injection of toxoid, recognized two major regions within residues 897-915 and 939-957. After multiple inoculations with toxoid, T cells of Balb/c expanded their recognition ability and responded very well to challenge with peptide 1261-1279 and moderately to stimulation with peptide 1149-1167. Unlike Balb/c T cells, those of toxoid-primed SJL (H-2s) mice exhibited a more complex profile and responded to challenge with a large number of overlapping peptides. After one toxoid injection, however, three peptides, 897-915, 939-957/953-971 overlap and 1051-1069, were the most potent T cells stimulators. After three toxoid injections, peptides 897-915 and 1051-1069 remained immunodominant while the third region was shifted upstream to 925-943/939-957 overlap. The immunodominant epitope within peptide 897-915 was recognized exclusively by T cells, since no Abs were detected against this region. The Ab binding profiles of the two mouse strains were quite similar, showing only small quantitative differences. Both, Balb/c and SJL anti-toxoid Abs displayed strong binding mainly to peptide 1177-1195, followed by peptides 869-887/883-901 overlap and 1275-1296. In addition, a significant amount of Balb/c anti-toxoid Abs was bound to peptide 1135-1153. Unlike Balb/c Abs, that interacted weakly with peptides 995-1013 and 1051-1069, the anti-toxoid Abs of SJL mice exhibited strong binding toward both peptides. The results showed that, in a given strain, the regions recognized by anti-toxoid Abs and T cells may coincide or may be uniquely B or T cell determinants.

Crit Rev Immunol. 1999;19(3):219-60. Related Articles, Links

Structure, activity, and immune (T and B cell) recognition of botulinum neurotoxins.

Atassi MZ, Oshima M.

Department of Biochemistry, Baylor College of Medicine, Houston, Texas 77030, USA.

Botulism, which was first reported over a century ago, is caused by botulinum neurotoxins produced by Clostridium botulinum in seven immunological serotypes (A through G). The primary structures of a number of these BoNTs have been determined and are reviewed here, together with their gene structure and synthesis. The biological actions of BoNTs, which result in their ability to block neurotransmitter release have been the subject of intensive study, and in this review we discuss the binding of BoNTs to the cell surface as well as the mechanism of their intercellular action. The ability of BoNTs to block neurotransmitter release has been exploited in therapeutic applications to reduce muscle hyperactivity for the treatment of a variety of clinical conditions associated with involuntary muscle spasm and contractions. The advantages, limitations, and risks of these applications are discussed. Certain compounds provide some limited protection against BoNT. However, more effective protection has been obtained immunologically either by passive immunity (i.e., by administration of anti-BoNT Abs) or by immunization with inactivated toxin. More recently, excellent protection has been obtained by immunization with the receptor-binding region comprising the C-terminal (residues 860 to 1296) fragment (Hc) of the heavy chain of BoNT/A. Here we review the mapping of the epitopes on the Hc region of BoNT/A that are recognized by anti-BoNT/A Abs raised in horse, human, and mouse. The epitopes on the Hc that are recognized by anti-Hc Abs and by Hc-primed T lymphocytes were mapped in two mouse strains [BALB/c (H-2d) and SJL (H-2s)]. The peptides, which contain Ab or T cell epitopes (or both) on the Hc, were used as immunogens in BALB/c and SJL mice and we identified those peptides whose Ab and/or T-cell response cross-react with Hc. Identification of these peptides is an important first step in the intricate requirements for the design of a synthetic vaccine.

Publication Types:
- Review

PMID: 10422600 [PubMed - indexed for MEDLINE]

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Ref   Items   RT  Index-term
E1       91      BOTULINUM ANTITOXIN --THERAPEUTIC USE --TU
E2        1      BOTULINUM ANTITOXIN --TOXICITY --TO
E3        0     *BOTULINUM TOXIN
E4     1907    4  BOTULINUM TOXIN TYPE A
E5      695       BOTULINUM TOXIN TYPE A --ADMINISTRATION AND DO
E6      279       BOTULINUM TOXIN TYPE A --ADVERSE EFFECTS --AE
E7       17       BOTULINUM TOXIN TYPE A --ANALYSIS --AN
E8       27       BOTULINUM TOXIN TYPE A --ANTAGONISTS AND INHIB
E9        9       BOTULINUM TOXIN TYPE A --BIOSYNTHESIS --BI
E10       5       BOTULINUM TOXIN TYPE A --BLOOD --BL
E11       3       BOTULINUM TOXIN TYPE A --CHEMICAL SYNTHESIS --
E12      67       BOTULINUM TOXIN TYPE A --CHEMISTRY --CH

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E13       2  BOTULINUM TOXIN TYPE A --CLASSIFICATION --CL
E14      14  BOTULINUM TOXIN TYPE A --CONTRAINDICATIONS --C
E15      21  BOTULINUM TOXIN TYPE A --ECONOMICS --EC
E16      36  BOTULINUM TOXIN TYPE A --GENETICS --GE
E17      12  BOTULINUM TOXIN TYPE A --HISTORY --HI
E18      63  BOTULINUM TOXIN TYPE A --IMMUNOLOGY --IM
E19      26  BOTULINUM TOXIN TYPE A --ISOLATION AND PURIFIC
E20      65  BOTULINUM TOXIN TYPE A --METABOLISM --ME
E21      23  BOTULINUM TOXIN TYPE A --PHARMACOKINETICS --PK
E22     266  BOTULINUM TOXIN TYPE A --PHARMACOLOGY --PD
E23       6  BOTULINUM TOXIN TYPE A --POISONING --PO
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Ref   Items   RT  Index-term
E25       1      BOTULINUM TOXIN TYPE A --SUPPLY AND DISTRIBUTI
E26    1080      BOTULINUM TOXIN TYPE A --THERAPEUTIC USE --TU
E27      37      BOTULINUM TOXIN TYPE A --TOXICITY --TO
E28       1      BOTULINUM TOXIN TYPE A --URINE --UR
E29     214      BOTULINUM TOXIN TYPE B
E30     113      BOTULINUM TOXIN TYPE C
E31      26      BOTULINUM TOXIN TYPE D
E32      72      BOTULINUM TOXIN TYPE E
E33      31      BOTULINUM TOXIN TYPE F
E34       1      BOTULINUM TOXIN TYPE G
E35    4435   11  BOTULINUM TOXINS
E36     775      BOTULINUM TOXINS --ADMINISTRATION AND DOSAGE -
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R3      4435    X       DC=D24.185.926.640.75. (BOTULINUM TOXINS)
R4       173    X    1  BOTULIN
R5         0    X    1  CLOSTRIDIUM BOTULINUM TOXINS
R6      2428    R   10  BOTULISM
R7       950    R  109  CHOLINERGIC AGENTS
R8      1949    R   11  CLOSTRIDIUM BOTULINUM
R9       594    B   29  ANTI-DYSKINESIA AGENTS
R10    14633    B   17  BACTERIAL TOXINS
R11     9560    B   15  NEUROTOXINS
R12     1907    N    4  BOTULINUM TOXIN TYPE A
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            80931  EPITOP?
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      S2       64  S1 AND (EPITOP? (3N) MAP?)
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      S3       15  S2 AND BOTULINUM?
? t s3/9/all
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15250118 PMID: 15027061

Deciphering antibody properties that lead to potent botulinum neurotoxin neutralization.

Marks James D

Department of Anesthesia and Pharmaceutical Chemistry, University of California, San Francisco General Hospital, San Francisco, California 94110, USA. marksj@anesthesia.ucsf.edu

Movement disorders - official journal of the Movement Disorder Society (United States) Mar 2004, 19 Suppl 8 pS101-8, ISSN 0885-3185
Journal Code: 8610688

Contract/Grant No.: R21 AI53389-01; AI; NIAID; U01 AI056493; AI; NIAID

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Monoclonal antibodies (mAbs) have been developed that bind to the toxin binding domain (H(C)) of **botulinum** toxin type A. These mAbs recognize with high affinity nonoverlapping epitopes on native toxin. The potency of a combination of three of the mAbs is almost 100 times greater than that reported for human polyclonal **botulinum** immune globulin. Potency appears to result largely from a marked increase in binding affinity for toxin that results when antibodies are combined. Precise epitope, or even domain recognized, seems to be of much less importance. The very high affinity required for toxin neutralization suggests why single mAbs that potently neutralize toxin have not been reported. Such affinities are not typically generated by the immune response. Copyright 2004 Movement Disorder Society (33 Refs.)

Tags: Research Support, U.S. Gov't, Non-P.H.S.; Research Support, U.S. Gov't, P.H.S.

Descriptors: *Antibodies, Monoclonal--immunology--IM; *Antigen-Antibody Reactions--physiology--PH; * **Botulinum** Toxin Type A--immunology--IM; *Neuromuscular Agents--immunology--IM; Animals; Antibodies, Monoclonal --pharmacology--PD; Antibody Specificity; **Botulinum** Toxin Type A --pharmacology--PD; **Botulism** --prevention and control--PC; Dose-Response Relationship, Drug; Drug Synergism; Enzyme-Linked Immunosorbent Assay --methods--MT; **Epitope Mapping** ; Humans; Lethal Dose 50; Neuromuscular Agents--pharmacology--PD; **Neurotoxins** --metabolism--ME; Neutralization Tests--methods--MT

CAS Registry No.: 0 (Antibodies, Monoclonal); 0 (Botulinum Toxin Type A); 0 (Neuromuscular Agents); 0 (Neurotoxins)

Record Date Created: 20040317

Record Date Completed: 20040615

14143922 PMID: 11926732

Characterisation of monoclonal antibodies against haemagglutinin associated with Clostridium botulinum type C neurotoxin.

Mahmut Nazira; Inoue Kaoru; Fujinaga Yukako; Hughes Lynn; Arimitsu Hideyuki; Sakaguchi Yoshihiko; Ohtsuka Aiji; Murakami Takuro; Yokota Kenji; Oguma Keiji

Department of Bacteriology, Okayama University Graduate School of Medicine, Japan.

Journal of medical microbiology (England) Apr 2002, 51 (4) p286-94, ISSN 0022-2615 Journal Code: 0224131

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Of 11 monoclonal antibodies (MAbs) prepared against the non-toxic component of type C Clostridium **botulinum** 16S toxin to clarify the function of the non-toxic component, seven recognised HA1, three recognised HA3b and one recognised HA2. Results of **epitope mapping** indicated that three of the seven anti-HA1 MAbs recognised the region between amino acid residues 121 and 140 and four recognised the three-dimensional structure of HA1. Three anti-HA3b MAbs recognised different regions between (approximately) amino acids 405-430, 180-270 and 275-297. The ability of these MAbs to interfere with binding of 16S toxin or non-toxic component, HA1 or HA3b to erythrocytes and to intestine tissue sections of guinea-pig was observed. MAbs against HA3b and HA2 did not inhibit 16S toxin binding to either erythrocytes or epithelial cells, whereas some MAbs against HA1 did inhibit binding. The seven anti-HA1 MAbs can be classified into four groups based on their binding inhibition activities. The anti-HA1 MAbs that inhibited the binding of 16S toxin to the epithelial cells also neutralised or reduced the oral toxicity in mice, indicating that HA may play an important role in the absorption of the 16S toxin from the small intestine.

Tags: Female; Research Support, Non-U.S. Gov't

Descriptors: *Antibodies, Monoclonal--immunology--IM; * **Botulinum** Toxins --immunology--IM; *Hemagglutinins--immunology--IM; Animals; Antibodies, Monoclonal--classification--CL; **Bacterial Toxins** --immunology--IM; Blotting, Western; **Botulinum** Toxins--chemistry--CH; Endopeptidases --metabolism--ME; Enzyme-Linked Immunosorbent Assay; **Epitope Mapping** ; Erythrocytes--immunology--IM; Guinea Pigs; Hemagglutinins--chemistry--CH; Humans; Immune Sera--immunology--IM; Immunoglobulin G--classification--CL; Immunoglobulin G--immunology--IM; Intestines--immunology--IM; Mice; Mice, Inbred BALB C; Neutralization Tests; Rabbits

CAS Registry No.: 0 (16S toxin, Clostridium botulinum); 0 (Antibodies, Monoclonal); 0 (Bacterial Toxins); 0 (Botulinum Toxins); 0 (Hemagglutinins); 0 (Immune Sera); 0 (Immunoglobulin G); 0 (botulinum toxin type C)

Enzyme No.: EC 3.4.- (Endopeptidases)

Record Date Created: 20020402

Record Date Completed: 20020403

11684961 PMID: 9014296

Mapping of protective and cross-reactive domains of the type A neurotoxin of Clostridium botulinum .

Dertzbaugh M T; West M W

Toxinology Division, U.S. Army Medical Research Institute of Infectious Diseases, Frederick, MD 21702-5011, USA.

Vaccine (ENGLAND) Nov 1996, 14 (16) p1538-44, ISSN 0264-410X Journal Code: 8406899

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

The purpose of this study was to identify the location of domains within the serotype A neurotoxin of Clostridium **botulinum** (BoNT/A) that conferred protection against **botulism** . The BoNT/A gene was subcloned into a series of 10 overlapping fragments that were expressed in Escherichia coli. The expressed proteins were partially purified and used to immunize mice. The resulting antisera were screened by immunoblotting analysis for the presence of BoNT/A-specific antibody. All fragments, except one, elicited antibody that recognized BoNT/A in an immunoblot. Serological screening identified several fragment-specific cross-reactive epitopes that were shared by heterologous serotypes of BoNT. Most of these epitopes immunoreactive by enzyme-linked immunosorbent assay, but not by immunoblot. Only two fragments were shown to confer protection against BoNT/A intoxication. Both of these proteins were derived from segments of the heavy chain and encoded amino acid residues H455-661 and H1150-1289 of BoNT/A.

Tags: Female

Descriptors: ***Botulinu** m Toxin Type A--immunology--IM; * **Clostridium botulinum --immunology** --IM; * **Epitope Mapping** --methods--MT; Animals; **Botulinum** Toxin Type A--biosynthesis--BI; **Botulinum0** Toxin Type A --isolation and purification--IP; **Botulism** --prevention and control--PC; Cross Reactions; Enzyme-Linked Immunosorbent Assay; Immunoblotting; Mice; Mice, Inbred C57BL; Protein Structure, Tertiary

CAS Registry No.: 0 (Botulinum Toxin Type A)

Record Date Created: 19970401

Record Date Completed: 19970401

11962308 PMID: 9246568

Localization of the regions on the C-terminal domain of the heavy chain of botulinum A recognized by T lymphocytes and by antibodies after immunization of mice with pentavalent toxoid.

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Immunological investigations (UNITED STATES) Jun 1997, 26 (4) p491-504, ISSN 0882-0139 Journal Code: 8504629

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Subfile: INDEX MEDICUS

We have mapped the regions recognized by T and/or B cells (Abs) on the C-terminal domain (Hc) of the heavy chain of **botulinum** neurotoxin serotype A (BoNT/A) after immunization of two inbred mouse strains with pentavalent toxoid (BoNTs A, B, C, D and E). Using a set of synthetic overlapping peptides, encompassing the entire Hc domain (residues 855-1296), we demonstrated that T cells of Balb/c (H-2d) mice, primed with one injection of toxoid, recognized two major regions within residues 897-915 and 939-957. After multiple inoculations with toxoid, T cells of Balb/c expanded their recognition ability and responded very well to challenge with peptide 1261-1279 and moderately to stimulation with peptide 1149-1167. Unlike Balb/c T cells, those of toxoid-primed SJL (H-2s) mice exhibited a more complex profile and responded to challenge with a large number of overlapping peptides. After one toxoid injection, however, three peptides, 897-915, 939-957/953-971 overlap and 1051-1069, were the most potent T cells stimulators. After three toxoid injections, peptides 897-915 and 1051-1069 remained immunodominant while the third region was shifted upstream to 925-943/939-957 overlap. The immunodominant epitope within peptide 897-915 was recognized exclusively by T cells, since no Abs were detected against this region. The Ab binding profiles of the two mouse strains were quite similar, showing only small quantitative differences. Both, Balb/c and SJL anti-toxoid Abs displayed strong binding mainly to peptide 1177-1195, followed by peptides 869-887/883-901 overlap and 1275-1296. In addition, a significant amount of Balb/c anti-toxoid Abs was bound to peptide 1135-1153. Unlike Balb/c Abs, that interacted weakly with peptides 995-1013 and 1051-1069, the anti-toxoid Abs of SJL mice exhibited strong binding toward both peptides. The results showed that, in a given strain, the regions recognized by anti-toxoid Abs and T cells may coincide or may be uniquely B or T cell determinants.

Tags: Female; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, Non-P.H.S.

13456876 PMID: 10422600

Structure, activity, and immune (T and B cell) recognition of botulinum neurotoxins .

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Critical reviews in immunology (UNITED STATES) 1999, 19 (3) p219-60, ISSN 1040-8401 Journal Code: 8914819

Publishing Model Print

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Main Citation Owner: NLM

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Subfile: INDEX MEDICUS

Botulism , which was first reported over a century ago, is caused by **botulinum neurotoxins** produced by Clostridium **botulinum** in seven immunological serotypes (A through G). The primary structures of a number of these BoNTs have been determined and are reviewed here, together with their gene structure and synthesis. The biological actions of BoNTs, which result in their ability to block neurotransmitter release have been the subject of intensive study, and in this review we discuss the binding of BoNTs to the cell surface as well as the mechanism of their intercellular action. The ability of BoNTs to block neurotransmitter release has been exploited in therapeutic applications to reduce muscle hyperactivity for the treatment of a variety of clinical conditions associated with involuntary muscle spasm and contractions. The advantages, limitations, and risks of these applications are discussed. Certain compounds provide some limited protection against BoNT. However, more effective protection has been obtained immunologically either by passive immunity (i.e., by administration of anti-BoNT Abs) or by immunization with inactivated toxin. More recently, excellent protection has been obtained by immunization with the receptor-binding region comprising the C-terminal (residues 860 to 1296) fragment (Hc) of the heavy chain of BoNT/A. Here we review the **mapping** of the **epitopes** on the Hc region of BoNT/A that are recognized by anti-BoNT/A Abs raised in horse, human, and mouse. The epitopes on the Hc that are recognized by anti-Hc Abs and by Hc-primed T lymphocytes were mapped in two mouse strains [BALB/c (H-2d) and SJL (H-2s)]. The peptides, which contain Ab or T cell epitopes (or both) on the Hc, were used as immunogens in BALB/c and SJL mice and we identified those peptides whose Ab and/or T-cell response cross-react with Hc. Identification of these peptides is an important first step in the intricate requirements for the design of a synthetic vaccine. (27 Refs.)

Descriptors: *B-Lymphocytes--immunology--IM; * **Botulinum** Toxins --immunology--IM; *T-Lymphocytes--immunology--IM; Amino Acid Sequence; Animals; **Botulinum** Toxins--chemistry--CH; **Botulinum** Toxins--poisoning --PO; Humans; Immunity, Cellular; Molecular Sequence Data; Poisoning--drug therapy--DT; Sequence Homology, Amino Acid

CAS Registry No.: 0 (Botulinum Toxins)

13869716 PMID: 11553596

Epitope mapping **of neutralizing** botulinum **neurotoxin A antibodies by phage display.**

Mullaney B P; Pallavicini M G; Marks J D

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Infection and immunity (United States) Oct 2001, 69 (10) p6511-4, ISSN 0019-9567 Journal Code: 0246127

Publishing Model Print

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Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Single-chain antibodies neutralize activity and bind nonoverlapping epitopes of **botulinum** A neurotoxin. Two phage display epitope libraries were constructed from the 1.3 kb of binding domain cDNA. The minimal epitopes selected against the single-chain Fv-Fc antibodies correspond to conformational epitopes with amino acid residues 1115 to 1223 (S25), 1131 to 1264 (3D12), and 889 to 1294 (C25).

Tags: Research Support, U.S. Gov't, Non-P.H.S.

Descriptors: *Antibodies, Bacterial--immunology--IM; * **Botulinum** Toxin Type A--immunology--IM; * **Clostridium botulinum --immunology** --IM; *Epitopes, B-Lymphocyte--immunology--IM; *Immunoglobulin Fragments --immunology--IM; *Immunoglobulin Variable Region--immunology--IM; Animals; **Botulinum** Toxin Type A--chemistry--CH; **Botulinum** Toxin Type A --genetics--GE; **Epitope Mapping** --methods--MT; **Epitopes** , B-Lymphocyte --chemistry--CH; Epitopes, B-Lymphocyte--genetics--GE; Humans; Mice; Models, Molecular; Neutralization Tests; Peptide Library; Protein Structure, Tertiary

CAS Registry No.: 0 (Antibodies, Bacterial); 0 (Botulinum Toxin Type A); 0 (Epitopes, B-Lymphocyte); 0 (Immunoglobulin Fragments); 0 (Immunoglobulin Variable Region); 0 (Peptide Library); 0 (immunoglobulin Fv)

Record Date Created: 20010912

Record Date Completed: 20011025

14085710 PMID: 11858873

Genetic and immunological comparison of anti- botulinum type A antibodies from immune and non-immune human phage libraries.

Amersdorfer Peter; Wong Cindy; Smith Theresa; Chen Steven; Deshpande Sharad; Sheridan Robert; Marks James D

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Vaccine (England) Feb 22 2002, 20 (11-12) p1640-8, ISSN 0264-410X Journal Code: 8406899

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

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Subfile: INDEX MEDICUS

Understanding the antibody response in **botulinum** intoxication is important for vaccine design and passive prophylaxis. To investigate this activity, we have studied the immune response to BoNT/A (**botulinum** neurotoxin serotype A) binding domain (HC) at the molecular level using phage display. The scFv antibodies were isolated from V-gene repertoires prepared from (a) human volunteer immunized with pentavalent **botulinum** toxoid and (b) non-immune human peripheral blood lymphocytes and spleenocytes. A large panel of serotype specific phage expressing **botulinum** binding scFv could be selected from both libraries. **Epitope mapping** of immune scFv binders towards BoNT/A HC revealed surprisingly a limited number of scFv recognizing conformational epitopes that corresponded to two distinct groups, clusters I and II. Only scFv from cluster I exhibited neutralizing activity in the mouse hemidiaphragm assay. Anti- BoNT/A HC clones derived from a non-immune library could be conveniently grouped into clusters III-XI and appeared to share no overlapping epitopes with cluster I or II. In addition they showed no neutralization of toxin at biologically significant concentrations. We therefore suggest that a vaccine based on the pentavalent **botulinum** toxoid directs the humoral immune response to a limited number of immunodominant epitopes exposed on the binding domain HC.

Tags: Comparative Study; Research Support, U.S. Gov't, Non-P.H.S.

Descriptors: *Antibodies, Bacterial--genetics--GE; *Antibodies, Bacterial--immunology--IM; * **Botulinum** Toxin Type A--immunology--IM; Antibodies, Monoclonal--genetics--GE; Antibodies, Monoclonal--immunology --IM; **Botulinum** Toxin Type A--toxicity--TO; **Botulism** --immunology--IM; **Botulism** --prevention and control--PC; **Botulism** --therapy--TH; **Clostridium botulinum** --immunology --IM; **Epitope Mapping** ; Humans; Immunoglobulin Variable Region--genetics--GE; Immunoglobulin Variable Region--immunology--IM; Neutralization Tests; Peptide Library

CAS Registry No.: 0 (Antibodies, Bacterial); 0 (Antibodies, Monoclonal); 0 (Botulinum Toxin Type A); 0 (Immunoglobulin Variable Region); 0 (Peptide Library)

Record Date Created: 20020222

11655947 PMID: 8968960

Mapping of the antibody-binding regions on botulinum neurotoxin H-chain domain 855-1296 with antitoxin antibodies from three host species.

Atassi M Z; Dolimbek B Z; Hayakari M; Middlebrook J L; Whitney B; Oshima M

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Journal of protein chemistry (UNITED STATES) Oct 1996, 15 (7) p691-700, ISSN 0277-8033 Journal Code: 8217321

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Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Subfile: INDEX MEDICUS

Botulism due to food poisoning is caused mainly by protein toxins, **botulinum neurotoxins** (BoNTs), produced by Clostridium botluinum in seven known immunological serotypes. These are the most potent toxins and poisons known. BoNT effects blockade of neuromuscular transmission by preventing neurotransmitter release. Human **botulism** is most frequently caused by types A, B, and E. Recent studies have shown that immunization with a 43-kDa C-terminal fragment (Hc, residues 860-1296) of BoNT/A affords excellent protection against BoNT/A poisoning. We raised antibodies (Abs) against BoNT/A in horse, and against pentavalent toxoid (BoNTs A, B, C, D, E) in human volunteers and outbred mice. Thirty-one 19-residue peptides that started at residue 855, overlapped consecutively by 5 residues, and encompassed the entire length of the Hc of BoNT/A were synthesized and used for mapping the Ab-binding regions recognized by the anti-BoNT/A antisera. Horse Abs against BoBT/A were bound by peptides 855-873, 939-957, 1079-1097/1093-1111 overlap, 1191-1209/1205-1223 overlap, 1261-1279 and 1275-1296. In addition, peptides 883-901, 911-929, 995-1013, 1023-1041/1037-1055 overlap, 1121-1139, and 1149-1167 gave low, but significant and reproducible, binding. With human antisera, high amounts of Abs were bound by peptides 869-887, 925-943, 981-999, 995-1013, 1051-1069, and 1177-1195. In addition, lower amounts of Abs were bound by peptides 911-929, 939-957, 967-985, and the overlaps 1121-1139/1135-1153 and 1247-1265/1261-1279/1275-1296. With outbred mouse antisera, high amounts of Abs were bound by peptides 869-887, 1051-1069, and 1177-1195, while peptides 939-957, 995-1013, 1093-1111, and 1275-1296 bound lower amounts of Abs. The results indicate that horse antiserum against BoNT/A or human and mouse (outbred) antisera against the toxoid recognized similar regions on BoNT/A, but exhibited some boundary frame shifts and differences in immunodominance of these regions among the antisera. Selected synthetic epitopes will be used as immunogens to stimulate active or passive (by Ab transfer) immunity against toxin poisoning.

Tags: Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, Non-P.H.S.

13561306 PMID: 11119555

High-affinity, protective antibodies to the binding domain of botulinum neurotoxin type A.

Pless D D; Torres E R; Reinke E K; Bavari S

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Infection and immunity (UNITED STATES) Jan 2001, 69 (1) p570-4, ISSN 0019-9567 Journal Code: 0246127

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Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

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Monoclonal antibodies (MAbs) were prepared against the putative binding domain of **botulinum** neurotoxin A (BoNT/A), a nontoxic 50-kDa fragment. Initially, all fusion products were screened against the holotoxin BoNT/A and against the binding fragment, BoNT/A H(C). Eleven neutralizing hybridomas were cloned, and their specific binding to BoNT/A H(C) was demonstrated by surface plasmon resonance, with dissociation constants ranging from 0.9 to <0.06 nM. **Epitope mapping** by real-time surface plasmon resonance showed that the antibodies bound to at least two distinct regions of the BoNT/A H(C) fragment. These MAbs will be useful tools for studying BoNT/A interactions with its receptor, and they have potential diagnostic and therapeutic applications.

Descriptors: *Antibodies, Bacterial--immunology--IM; *Antibodies, Monoclonal--immunology--IM; *Antibody Affinity; * **Botulinum** Toxins --immunology--IM; Animals; Antibodies, Monoclonal--biosynthesis--BI; Binding Sites; Biosensing Techniques; Enzyme-Linked Immunosorbent Assay; **Epitope Mapping** ; Mice; Mice, Inbred BALB C; Vaccination

CAS Registry No.: 0 (Antibodies, Bacterial); 0 (Antibodies, Monoclonal); 0 (Botulinum Toxins)

Record Date Created: 20010118

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